IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

IN RE: ZOSTAVAX (ZOSTER VACCINE LIVE) PRODUCTS LIABILITY LITIGATION	:	MDL NO. 2848 CIVIL ACTION NO. 18-md-2848
THIS DOCUMENT RELATES TO: JOSEPH BOCKUS v. MERCK & CO., INC., et al. Civil Action No. 18-20020	:	

MEMORANDUM IN SUPPORT OF PRETRIAL ORDER NO. 508

Bartle, J. October 11, 2023

Plaintiff Joseph Bockus has sued defendants Merck & Co., Inc. and Merck Sharp & Dohme Corp. ("Merck") in this product liability action. Mr. Bockus alleges that he developed Guillian-Barré syndrome ("GBS") as a result of being inoculated with Zostavax, a vaccine developed by defendants to prevent shingles.[1] This action, which is part of Multidistrict Litigation No. 2848, has been selected as a bellwether case for trial. Before the court is the motion of defendants to exclude the general causation opinion of plaintiff's expert Mark

1. Mr. Bockus presently asserts claims for negligence and strict liability design defect. He has stipulated to dismiss claims for negligent manufacturing, strict liability manufacturing defect, breaches of express and implied warranty, negligent misrepresentation, unjust enrichment, negligent failure to warn, and strict liability failure to warn.

Poznansky, M.D., and the general and specific causation opinions of plaintiff's expert David Saperstein, M.D., on the ground that the opinions fail to meet the standard required under Rule 702 of the Federal Rules of Evidence[2] and Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993).

I

Rule 702 of the Federal Rules of Evidence provides that:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
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> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
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> (b) the testimony is based on sufficient facts or data;
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> (c) the testimony is the product of reliable principles and methods; and
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> (d) the expert has reliably applied the principles and methods to the facts of the case.

Our Court of Appeals has described Rule 702 as requiring expert testimony to meet three criteria: (1) qualification, (2) reliability, and (3) fit. See, e.g.,

2. Defendants also cite Rules 401 and 403 of the Federal Rules of Evidence to support their motion. Rule 401 provides the test for relevance, and Rule 403 allows the court to exclude relevant evidence for prejudice, confusion, waste of time, or other reasons.

Schneider ex rel. Estate of Schneider v. Fried, 320 F.3d 396, 404 (3d Cir. 2003).

The court operates in a "gatekeeping role" that ensures that the testimony "both rests on a reliable foundation and is relevant to the task at hand." Daubert, 509 U.S. at 597. This gatekeeping prevents opinion testimony that does not meet these requirements from reaching the jury. Schneider, 320 F.3d at 404. The party presenting the expert need not show that the opinions of the expert are correct but rather by a preponderance of the evidence that the opinions of the expert are reliable. In re Paoli R.R. Yard PCB Litig., 35 F.3d 717, 744 (3d Cir. 1994). This inquiry under Rule 702 is a "flexible one" that is focused "solely on principles and methodology, not on the conclusions that they generate." Daubert, 509 U.S. at 594-95. Instead, "[t]he analysis of the conclusions themselves is for the trier of fact when the expert is subjected to cross-examination." Kannankeril v. Terminix Int'l, Inc., 128 F.3d 802, 807 (3d Cir. 1997).

II

Mr. Bockus was inoculated with Zostavax on August 14, 2014. He was 50 years old at the time. Three days later, he began experiencing fatigue and a tingling sensation in his arms and feet. He later began experiencing progressive weakness, numbness in his hands, back pains, and delayed reflexes. He was

admitted to a hospital where he was diagnosed with a suspected case of GBS. His condition responded well to intravenous immunoglobulin treatment. His strength and function improved, and he regained his reflexes. However, he still experiences weakness in his lower extremities.

GBS is a relatively rare autoimmune disorder that causes the body's immune system to attack its own nerves. Symptoms of GBS include limb and cranial nerve weakness often with respiratory compromise and limitation on physical function. In the United States there are between one and two cases of GBS per year for every 100,000 people. The cause of GBS is not well understood. The National Institute for Neurological Disorders and Stroke reports that GBS tends to appear "days or weeks following a respiratory or gastrointestinal infection." Guillain-Barré Syndrome, Nat'l Inst. of Neurological Disorders & Stroke, https://www.ninds.nih.gov/health-information/disorders/guillain-barre-syndrome (July 31, 2023). It is undisputed that the cause is unknown in approximately one-third of the cases of GBS. See Deposition of David Saperstein, M.D., at 128:9-14 (May 3, 2023); see also Nicola Luigi Braggazi et al., Global, Regional, and National Burden of Guillain-Barré Syndrome and its Underlying Causes from 1990 to 2019, 18 J. Neuroinflamm. 264, at 275 fig.5 (2021).

III

Dr. Poznansky is a professor at Harvard Medical School and has practiced in the field of infections, diseases, and immunology for almost four decades. For more than a decade, he has served as the Director of the Vaccine and Immunotherapy Center at Massachusetts General Hospital.

Dr. Saperstein is a physician who is board-certified in neurology and neuromuscular medicine and a Professor of Neurology at the University of Arizona Medical Center. He has twenty-five years of experience studying and treating immune-mediated neuropathies such as GBS.

Defendants do not challenge the qualifications of either Dr. Poznansky or Dr. Saperstein. They also do not challenge the fit of their opinions. Rather, defendants focus their Daubert motion on the reliability of the methods these physicians employed in reaching their causation opinions.

IV

Dr. Saperstein and Dr. Poznansky both offer a general causation opinion: that inoculation with Zostavax is capable of causing individuals to develop GBS. Their opinions are substantively similar, although they diverge slightly in the methods used in reaching them.

Both opine that Zostavax causes GBS through a process known as molecular mimicry. Zostavax is a live-attenuated

vaccine, that is it works by introducing diluted viral cells to provoke the body's immune system to respond by creating antibodies. The theory of molecular mimicry hypothesizes that a live-attenuated virus can cause the immune system to create not only antibodies that respond to that virus but also proteins that attack one's own immune system. Dr. Poznansky and Dr. Saperstein rely on medical literature that purportedly supports the existence of molecular mimicry as well as studies which conclude that molecular mimicry can cause an individual to contract GBS.

Defendants counter that the theory of molecular mimicry demonstrates only biological plausibility, which is insufficient to prove general causation absent epidemiological support. Further, both Dr. Poznansky and Dr. Saperstein concede that while molecular mimicry is a theory, they could not identify a particular component of Zostavax that would trigger this mechanism. Dr. Saperstein is more specific regarding the mechanisms by which molecular mimicry could occur, citing Bianca Oliveri et al., Review, Vaccinations and Autoimmune Diseases, Vaccines, 2021, at 815. There are no epidemiological studies that support the theory that molecular mimicry occurs in the case of the Zostavax vaccine.

The parties describe epidemiological studies as the "gold standard" for proving general causation. In re Zoloft

(Sertraline Hydrochloride) Prods. Liab. Litig., 26 F. Supp. 3d 466, 475 (E.D. Pa. 2014). Such studies compare the risk or rate of a disease or condition in a group exposed to a certain substance to the rate in a group not exposed. For the comparison to be scientifically valid, the control group must be properly selected. In re Diet Drugs (Phentermine, Fenfluramine, Dexfenfluramine) Prods. Liab. Litig., MDL No. 1203, 2000 WL 962545, at *6 (E.D. Pa. June 28, 2000).

Dr. Poznansky and Dr. Saperstein relied on an epidemiological study comparing the incidence of GBS following inoculation with Zostavax to that of Shingrix, another shingles vaccine. Ravi Goud et al., Risk of Guillain-Barré Syndrome Following Recombinant Zoster Vaccine in Medicare Beneficiaries, JAMA Internal Med., 2021 ("Goud study"). This study followed over time a group who had been inoculated with Zostavax and a group who had been inoculated with Shingrix in order to determine the relative risk of GBS after inoculation with Shingrix. The Goud study used Zostavax as a baseline to determine whether Shingrix carries a greater risk of causing GBS than Zostavax does. The study also reported the incidence of GBS in the general population: one to two cases in the United States per year per 100,000 persons. Id. at 2. No party contests this fact.

The study found that among individuals inoculated with Zostavax, GBS occurred in 9 individuals out of 75,340,000 person-days.[3] Id. at 5 tbl.2. During his deposition, Dr. Poznansky stated that this demonstrates a "calculable" risk of contracting GBS after inoculation with Zostavax. Plaintiff's counsel made this arithmetic calculation in their briefing: of those inoculated with Zostavax, GBS occurs at a rate of 4.36 cases per 100,000 persons per year, greater than the background rate of GBS in the unexposed population. Plaintiff's experts concede that no epidemiological study exists which directly compares the incidence of GBS in Zostavax recipients compared with a control group of the general public. However, Dr. Poznansky points out that an increased risk of GBS from a Zostavax inoculation is "calculable" based the Goud study's data and its stated rate of GBS in the general population. Thus, it is fair to infer that Dr. Poznansky relies on the Goud study for the proposition that GBS occurs two to four times more frequently following Zostavax than would be expected in the general population. This is sound methodology.

Defendants argue that plaintiff's experts ignored a study that investigated the relationship between Zostavax and

3. A person-day is a type of measurement in an epidemiological study that takes into account the number of people in the study and the length of time each person is studied.

autoimmune side effects, including GBS. Yi Chun Lai & Yik Weng Yew, Severe Autoimmune Adverse Events Post Herpes Zoster Vaccine: A Case-Control Study of Adverse Events in a National Database, 14 J. Drugs Derm. 681 (2015) ("Lai study"). It is true that neither Dr. Poznansky nor Dr. Saperstein references the Lai study in their expert reports. Nevertheless, both experts state in their responses and objections to their notices of deposition that they "disclose the review and analysis" of a list of documents including the Lai study.

The Lai study reviewed adverse events data in two populations, that is, individuals who had received Zostavax and individuals who had received a vaccine against tetanus but had not received Zostavax. The study concluded that the odds of contracting GBS from Zostavax "were not significantly increased post immunization." Id. at 683.

The reliability of the Lai study depends on its statement that "Tetanus toxoid-containing vaccines are not known to be associated with [serious autoimmune adverse events]," which includes GBS. Id. at 682. Otherwise, the comparison of the group inoculated with the tetanus vaccine and the group inoculated with Zostavax would not be reliable. A 2005 study that examined the risk for significant autoimmune adverse events following Hepatitis B vaccinations is cited in support of the

critical statement.[4] Plaintiff challenges the validity of this statement, as the Lai study does not take into account later Vaccine Court decisions before the Court of Federal Claims, which in applying a preponderance of the evidence standard, have regularly found a causal relationship between the tetanus toxoid vaccination and GBS.[5]

The parties spend much time arguing about the validity and persuasiveness of these studies. Neither study is so lacking as to demand that the court exercise its gatekeeping role to exclude one or both of them. It is not the role of the court at this stage to decide on the merits or demerits of the Goud study versus those of the Lai study. Kannankeril, 128 F. 3d at 809. The issue of the weight and credibility of the testimony of plaintiff's experts with regard to these studies

4. The study compared the risk of serious autoimmune adverse events for those inoculated with the Hepatitis B vaccine to a baseline: those inoculated with a tetanus toxoid-containing vaccine. David A. Geier et al., A Case-Control Study of Serious Autoimmune Adverse Events Following Hepatitis B Immunization, 38 Autoimmunity 295, 296 (2005). The study did not track the incidence of GBS in either population. Id. at 298 tbl.2.

5. See, e.g., Garcia v. Sec'y of Health & Hum. Servs., No. 05-720, 2008 WL 5068934, at *9 (Fed. Cl. Nov. 12, 2008); Harris v. Sec'y of Health & Hum. Servs., No. 18-944, 2023 WL 2583393, at *22 (Fed. Cl., Spec. Master Feb. 21, 2023); Mohamad v. Sec'y of Health & Hum. Servs., No. 16-1075, 2022 WL 711604, at *19 (Fed. Cl., Spec. Master Jan. 27, 2022); Watson v. Sec'y of Dep't of Health & Hum. Servs., No. 96-639, 2001 WL 1682537, at *1 (Fed. Cl., Spec. Master Dec. 18, 2001).

must be tested by cross-examination and ultimately, decided by the finder of fact.

Dr. Poznansky also relies on case reports in forming his opinion. These are narrative descriptions of individual adverse events that are perceived to have occurred in patients shortly after taking a prescription medicine. In re Zoloft (Setralinehydrochloride) Prods. Liab. Litig., 176 F. Supp. 3d 483, 497 (E.D. Pa. 2016). Such reports are "anecdotal evidence" and consist of "merely accounts of medical events." Id. Dr. Poznansky considered 38 adverse event reports compiled by Merck in which Merck acknowledges the existence of individuals who developed GBS after receiving Zostavax.[6] Defendants' internal documents reveal that the GBS in eight individuals "did not have other clear" or "more plausible alternative etiolog[ies]" than Zostavax. It is noteworthy that the Lai study incorporated this adverse event report data on which Dr. Poznansky relied, although the study reached a different conclusion--that is, that the adverse event reports do not support a link between Zostavax and GBS.

Case reports and adverse event reports are "universally recognized as insufficient and unreliable evidence of causation" in the absence of other reliable evidence. In re

6. Dr. Saperstein does not rely on these adverse event reports in reaching his general causation opinion.

Diet Drugs (Phentermine, Fenfluramine, Dexfenfluramine) Prods. Liab. Litig., MDL No. 1203, 2001 WL 454586, at *15 (E.D. Pa. Feb. 1, 2001). However, experts are frequently permitted to offer opinions that are based on case reports and adverse event reports as long as they are considered in conjunction with other evidence. E.g., In re Tylenol (Acetaminophen) Mktg., Sales Pracs., & Prods. Liab. Litig., MDL No. 2436, 2016 WL 3997046, at *9 (E.D. Pa. July 26, 2016); In re Diet Drugs (Phentermine/Fenfluramine/Dexfenfluramine) Prods. Liab. Litig., 890 F. Supp. 2d 552, 562 (E.D. Pa. 2012).

When experts rely only in part on case reports in forming causation opinions, their opinion should not be excluded for these reasons. See, e.g., Wolfe v. McNeil-PPC, Inc., Civ. A. No. 07-348, 2011 WL 1673805, at *5 (E.D. Pa. May 4, 2011). However, reliance on case reports should be minimized because they do not take into account the background rate of disease. Soldo v. Sandoz Pharms. Corp., 244 F. Supp. 2d 434, 540 (W.D. Pa. 2003). Therefore, their utility is limited.

Here, Dr. Poznansky's general causation opinion relies on epidemiological evidence to demonstrate a causal connection between Zostavax and GBS. Therefore, he is permitted to include case reports as one aspect of his opinion.

The court, of course, is not deciding whether the general causation opinions of Dr. Poznansky and Dr. Saperstein

are correct. Again, that decision is for a jury. It is sufficient for present purposes that they have used reliable methodology. These experts extrapolate from an epidemiological study based on widely accepted methods, and in the case of Dr. Poznansky, also utilizes case reports as only one element of his opinion. The plaintiff's experts meet the standards under Rule 702 and Daubert on general causation that Zostavax can cause GBS.

V

The court now turns to the opinion of Dr. Saperstein in which he concludes that Zostavax caused Mr. Bockus to develop GBS. Dr. Saperstein asserts that he performed a differential diagnosis to reach this conclusion. A differential diagnosis is the hallmark of internal medicine and is used to reach a diagnosis by ruling in conditions and ruling out alternative explanations for symptoms. Paoli, 35 F.3d at 756. As explained by our Court of Appeals in Kannankeril,

> We have recognized "differential diagnosis" as a technique that involves assessing causation with respect to a particular individual. Differential diagnosis is defined for physicians as "the determination of which of two or more diseases with similar symptoms is the one from which the patient is suffering, by a systematic comparison and contrasting of the clinical findings."

128 F.3d at 807 (citations omitted).

To perform a sufficiently reliable differential diagnosis, an expert must rule out, not all other possible causes, but only obvious alternative causes. Heller v. Shaw Indus., Inc., 167 F.3d 146, 156 (3d Cir. 1999). In excluding an alternative cause, the expert must provide "good grounds" for doing so. Paoli, 35 F.3d at 743. A physician may consider medical records, peer-reviewed literature and scientific studies as well as their own clinical experience in making this determination. See, e.g., Kannankeril, 128 F.3d at 807-09.

To rule in Zostavax as the cause of Mr. Bockus's GBS, Dr. Saperstein relies on the short temporal proximity of three days between when he received Zostavax and when his symptoms began. He also asserts that Mr. Bockus was experiencing immunosenescence, which means an individual's immune systems weakens with age. Mr. Bockus was 50 years old when he was inoculated with Zostavax. Dr. Saperstein posits that Mr. Bockus's weakened immune system made him more vulnerable to a Zostavax-caused infection, which in turn caused him to develop GBS. Dr. Saperstein also relies upon his own clinical experience of over 25 years working as a specialist in diagnosing and managing GBS. He has been involved with the care of over 100 patients with GBS. Even so, Dr. Saperstein concedes that contracting GBS less than one week after a triggering infection is unusual.

While temporal proximity alone is not an adequate bonus to support specific causation, it along with additional valid factors may be considered. Heller, 167 F.3d at 154-55. An expert's opinion cannot be considered reliable simply based on a post hoc ergo propter hoc analysis. In re Zostavax (Zoster Vaccine Live) Prods. Liab. Litig., 579 F. Supp. 3d 675, 683 (E.D. Pa. 2021) (citing McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1243 (11th Cir. 2005); Ohio v. U.S. Dep't of Interior, 880 F.2d 432, 473 (D.C. Cir. 1989)). Without more, Dr. Saperstein's "ruling in" of Zostavax because of his post hoc ergo proctor hoc reasoning as the cause of Mr. Bockus's GBS fails.

Dr. Saperstein rules out obvious known alternative causes of Mr. Bockus's GBS, but he does not rule out idiopathic, that is unknown or unexplained causes. When unexplained causes are common, a differential diagnosis is insufficient when it does not eliminate these causes. See, e.g., Pritchard v. Dow Argo Scis., 705 F. Supp. 2d 471, 492 (W.D. Pa. 2010), aff'd, 430 F. App'x 102 (3d Cir. 2011); Perry v. Novartis Pharms. Corp., 564 F. Supp. 2d 452, 469-70 (E.D. Pa. 2008). Dr. Saperstein admits that approximately one-third of cases of GBS result from unknown or unexplained causes. His own clinical experience demonstrates that one-half of the cases of GBS he has seen have idiopathic causes. When such a significant portion of cases are

idiopathic, the expert must exclude idiopathic causes to have a reliable opinion of a known cause. Lopez v. Wyeth-Ayerst Lab'ys, Civ. A. No. 94-4054, 1996 WL 784566 (N.D. Cal. Dec. 13, 1996), aff'd, 139 F.3d 905 (9th Cir. 1998).

Dr. Saperstein states in his expert report that there is "no evidence to reasonably suspect bacterial infection, trauma, recent surgery or organ transplantation, or a chronic underlying disease" contributed to his developing GBS. Simply stating that there is no evidence of these events is insufficient to eliminate idiopathic causes. Significantly, Dr. Saperstein conceded at his deposition that he did not rule out idiopathic causes of Mr. Bockus's GBS. Consequently, he does not have good grounds for his specific causation opinion that Zostavax caused Mr. Bockus's GBS. His opinion does not meet the reliability standards of Rule 702 and Daubert.

VI

Accordingly, the motion of Merck insofar as it seeks to exclude the general causation opinions of Mark Poznansky, M.D. and David Saperstein, M.D. is DENIED, but the motion insofar as it seeks to exclude the specific causation opinion of David Saperstein, M.D. is GRANTED.